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How I manage major hemorrhage

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Acute hemorrhage can be a life-threatening emergency that is complex in its management and affects many patient populations. The past 15 years has seen the introduction of comprehensive massive hemorrhage protocols, wider use of viscoelastic testing, new coagulation factor products, and the publication of robust randomized controlled trials in diverse bleeding patient populations. Although gaps continue to exist in the evidence base for several aspects of patient care, there is now sufficient evidence to allow for an individualized hemostatic response based on the type of bleeding and specific hemostatic defects. We present 3 clinical cases that highlight some of the challenges in acute hemorrhage management, focusing on the importance of interprofessional communication, rapid provision of hemostatic resuscitation, repeated measures of coagulation, immediate administration of tranexamic acid, and prioritization of surgical or radiologic control of hemorrhage. This article provides a framework for the clear and collaborative conversation between the bedside clinical team and the consulting hematologist to achieve prompt and targeted hemostatic resuscitation. In addition to providing consultations on the hemostatic management of individual patients, the hematology service must be involved in setting hospital policies for the prevention and management of patients with major hemorrhage.

Introduction

Hematology consultation during life-threatening hemorrhage is challenging because it is infrequent, often occurs outside of daytime hours, and requires immediate response, often without the opportunity for direct assessment of an unfamiliar patient. This article provides a framework for the consultative discussion, outlines pathways for laboratory and transfusion decision-making for varied patient populations, and highlights strategies to optimize care. The focus of the article is on life-threatening hemorrhage requiring both red blood cell (RBC) and hemostatic transfusion support (plasma, platelets, cryoprecipitate, and coagulation factor concentrates). Management of less severe bleeding, particularly gastrointestinal tract hemorrhage, is usually with restrictive RBC transfusions, with exceptional use of plasma, and thus rarely requires hematology consultation.[1-3] Recent US and international guidelines for gastrointestinal tract bleeding recommend the use of a restrictive hemoglobin threshold (7-8 g/dL) for both variceal and nonvariceal bleeding.[2,4,5] In terms of recommendations for the use of hemostatic transfusion support for patients with variceal bleeding, the guidelines highlight that bleeding is from portal hypertension (and not a bleeding diathesis) and that no thresholds for use of hemostatic products are recommended.[5] In a series of 53 836 massive transfusions (>10 units in 24 hours), the most common indications for massive transfusion were cardiac surgery (35%), noncardiac surgery (33%), traumatic injury (16%), and obstetrics (3%).[6] Major hemorrhages account for 5% of transfusions.[6] This article focuses on the management of hemorrhage in trauma, cardiac surgery, and obstetrics. The key contributors to the hemostatic derangement in these conditions are varied (Table 1). Given the diverse pathophysiological pathways that can lead to major hemorrhage, goal-directed, personalized care based on repeated laboratory assessments should be the primary strategy, and reliance on formula-based resuscitation (ratios of RBC to components) should be restricted to the early phase of hemorrhage while obtaining source control and awaiting results of laboratory tests of coagulation.[25]

Key management strategies during management of life-threatening hemorrhage

Quality improvement audits demonstrate it is a challenge to achieve high levels of compliance with massive hemorrhage protocols,[26,27] which is not surprising given the number and complexity of tasks that must be completed in the care of these patients. As such, the consulting hematologist should be astutely looking for strategies to optimize care to assist the bedside team to rapidly achieve hemostasis. Presented in Table 2 is a comprehensive list of key management strategies and suggested recovery tactics. Maintaining a collegial relationship with the interdisciplinary clinical team is essential for optimal patient outcomes. Thus, during these invariably brief

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Table 1. Brief overview of the key contributors to the hemostatic disturbance in cardiac surgery, traumatic injury, and obstetrical hemorrhage

Variable	Cardiac surgery[10-15]	Traumatic injury[16-18]	Obstetrics[19-24]
Endothelial injury	Disruption to the endothelial glycocalyx is thought to be part of the systemic inflammatory response to cardiopulmonary bypass	Disruption to the endothelial glycocalyx, leading to release of natural heparin sulfate, thrombomodulin exposure, activation of protein C, reduction in factors V/VIII, and release of tissue plasminogen activator	Levels of thrombomodulin and plasminogen activator inhibitor-1 increase during pregnancy
Fibrinogen	Reduced by half during on-pump cardiac surgery	Reduced	Fibrinogen levels increase throughout pregnancy, but are reduced in patients with postpartum hemorrhage
Fibrinolysis	Hyperfibrinolysis present	Hyperfibrinolysis present	Plasma fibrinolytic activity reduced at delivery; reduced lysis index in patients with postpartum hemorrhage
Thrombin generation	Thrombin generation reduced by half during on-pump cardiac surgery	Preserved	Enhanced thrombin potential increases throughout pregnancy, but is reduced in half in patients with postpartum hemorrhage
Coagulation factor levels	Reductions in factors V, X, XI, and XIII	Reduction in factors V and VIII	Coagulation factors VII, X, VIII, and VWF increase throughout pregnancy; levels in patients with postpartum hemorrhage are not different out to 4 h after hemorrhage
Platelet function	Thrombocytopenia and platelet dysfunction	Platelet dysfunction	Platelet activation in patients with preeclampsia

The hemostatic derangements for cardiac surgery,[7] traumatic injury,[8] and obstetrical hemorrhage[9] have been reviewed and provided in an illustrated format elsewhere.
VWF, von Willebrand factor.

interactions that take place over the telephone into an often tense operating room, the consulting hematologist must be professional and respectful but use an assertive communication style to ensure that the patient is provided an evidence-based hemostatic response.[44]

Rapidly expanding literature and clinical trial evidence

Over the past 15 years, several randomized controlled trials (RCTs) in the setting of major hemorrhage across different patient types have been published. These trials have provided clarity on what we should (or perhaps should not) be doing to improve the care of bleeding patients. RCTs have found tranexamic acid (TXA), especially within 60 minutes of injury or hemorrhage, to be of value in traumatic injury[34] and postpartum hemorrhage (PPH),[35] and prophylactically in cardiac surgery[45] and noncardiac surgery[36]; however, it is of little value (and potentially harmful) in patients with gastrointestinal tract bleeding.[37]

Several RCTs have explored the role of coagulation products as part of early resuscitation in trauma settings. In a prehospital cluster trial involving 27 US air medical bases, there was a 10% improvement in survival when they compared 230 trauma patients administered a median of 2 units of plasma with 271 patients who received only crystalloid and red cells based on local protocols.[46] Subsequently, 3 RCTs comparing prehospital transfusion (including plasma) with crystalloid in traumatic injury were conducted and failed to observe improvements in outcomes.[47-49] It has been hypothesized that prehospital plasma may have clinically important benefits in a subset of trauma patients, such as those with severe blunt injury, traumatic brain injury,[50] or longer transport times.[51] For trauma patients with severe bleeding in the emergency department, an RCT of 680 patients found no difference in mortality at 24 hours or 30 days when a 1:1:1 ratio of red cells to plasma to platelets was compared with a lower ratio of 2:1:1, but left residual uncertainty for other patient outcomes.[52,53]

The role of viscoelastic testing in bleeding management has also been studied in several settings. A cluster trial of viscoelastic testing and a transfusion algorithm in cardiac surgery showed a reduction in the rate of major bleeding[54]; however, a smaller RCT in traumatic injury, called Implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy (ITACTIC), found no improvements in outcomes for patients managed with viscoelastic testing, compared with standard laboratory testing, despite receiving hemostatic products earlier and in greater number.[55]

A large RCT of preemptive fibrinogen replacement in trauma, compared with fibrinogen replacement based on laboratory test results, found no improvement in patient outcomes.[56] Similarly, RCTs find preemptive fibrinogen replacement to be of no benefit in PPH.[57,58] For the type of fibrinogen replacement product, cryoprecipitate and fibrinogen concentrates have similar efficacy in cardiac surgery and trauma[33,59]; and, fibrinogen concentrate is cost-effective, compared with cryoprecipitate.[60] Investigators in the area of trauma are

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Table 2. Key management strategies for optimizing hemostatic management in patients with life-threatening hemorrhage

Issues	Management strategy
Identify patients at risk for hemorrhage	• In situations where a hemorrhage is not immediately recognized, the patient may have complete hemostatic failure at the point of apparent onset of hemorrhage o Examples include delayed recognition of PPH or delayed recognition of intra-abdominal hemorrhage after trauma (concealed retroperitoneal or pelvic hemorrhage) o In these situations, immediate and frequent tests of hemostasis are required to aggressively use hemostatic treatments to return coagulation factors, fibrinogen, and platelet counts to hemostatic levels • Patients with traumatic injury and life-threatening hemorrhage will usually have an INR >1.2 on arrival[28]; hence, it is critical for the consulting hematologist to be aware of the results of coagulation testing on arrival to the emergency department • In postpartum hemorrhage, patients who progress to a life-threatening hemorrhage are more likely to have a fibrinogen level of <2.0 g/L[29]
Recognize patients at high risk for hemostatic failure	• There are particular patients who are at high risk for hemostatic failure o These include patients with traumatic brain injury,[30] patients with cardiac arrest during hemorrhage resuscitation,[31,32] and preoperative critical state for surgical patients (eg, acute aortic dissection or cardiac arrest before cardiac surgery)[33]
Ensure timely administration of TXA	• TXA is a critical treatment for reducing mortality after traumatic injury,[34] reducing hemorrhagic deaths after postpartum hemorrhage,[35] and reducing major bleeding after surgery[36] • If the patient is within 3 h of injury or onset of hemorrhage and TXA has not been administered, it should be given as soon as possible (except in patients with gastrointestinal tract hemorrhage[37]) • TXA also assists in stabilizing the hemostatic derangement[38,39]
Ensure frequent measures of hemostasis	• Hemostatic testing should be performed at a minimum of every 30-60 minutes during active hemorrhage[40]; it should be preferably timed after each dose of hemostatic product • It is critical to determine the timing and results of the last set of laboratory tests o Complete testing includes either (1) standard laboratory tests with platelet count, PT/INR, PTT, and fibrinogen; or (2) viscoelastic testing (with platelet count)[41]
Facilitate rapid release of coagulation testing results	• If point-of-care viscoelastic testing is not used, the coagulation laboratory needs to have processes in place for immediate release of a rapid hemorrhage panel to expedite administration of targeted hemostatic treatments[42] o If the coagulation testing was sent >20 minutes ago and is not available, a call to the coagulation laboratory is required o Delays can occur when the preliminary result shows undetectable clot in the PT/INR, PTT, and fibrinogen, prompting additional repeats and dilutions. If an undetected clot is found, hemostatic resuscitation should not be delayed until definitive results are released.
Ensure rapid transition to goal-directed hemostatic resuscitation	• Formula-driven resuscitation is commonly used until laboratory testing is available to allow for personalization of the hemostatic transfusion response o Continued formula-driven resuscitation should rarely be used past the first 60 min • As can be seen in Table 1, the hemostatic disturbance is broad and highly variable to the patient clinical context • Plasma transfusion alone is not recommended, nor sufficient, for hypofibrinogenemia[25]
Personalize the hemostatic response	• Application of formula-driven resuscitation to all patient types and severity of hemorrhage is likely to lead to overtransfusion of some patients and underresuscitation of others • It is crucial to consider the underlying mechanism of the hemostatic derangement for the patient clinical setting to guide the laboratory testing plan and the hemostatic response
Assist with interpretation of viscoelastic testing	• Although viscoelastic testing has been around for >50 years, the results are more complex to interpret than the standard coagulation tests • If viscoelastic testing has been completed, the consulting hematologist should have the skill to interpret both the curves and numerical outputs to guide the bedside team on the hemostatic response[43]
Understand the plan for surgical control of hemorrhage	• The importance of obtaining definitive surgical control of hemorrhage cannot be overstated • The consulting hematologist should ensure there is a clear plan for surgical control of bleeding (eg, immediate hysterectomy, consultation of interventional radiology, and return to the operating room for surgical reexploration)

INR, international normalized ratio; PPH, postpartum hemorrhage; PT, prothrombin time; PTT, partial thromboplastin time; TXA, tranexamic acid.

continuing to study the differential effects on hemostatic laboratory tests after the administration of cryoprecipitate, compared with fibrinogen concentrates.[59,61] Prophylactic administration of 4-factor prothrombin complex concentrates (PCCs) as an adjunct to formula-based resuscitation failed to improve outcomes in trauma patients and increased the rate of thrombosis.[62] Early-stage RCTs comparing PCCs with plasma for hemorrhage after cardiac surgery suggest similar efficacy to

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plasma, and a large definitive trial has completed enrollment (NCT05523297).[63-65]

Role of the consultative hematologist

Given the urgency of the situation, a targeted conversation with the bedside team can help to rapidly understand the current (general and hemostatic) status of the patient, hemorrhage source control, and the hemostatic treatments to date (Table 3). This conversation will direct your suggestions for additional laboratory testing, transfusions (types and dosages), anticoagulant reversal, and hemostatic treatments. When certain hemostatic tests of coagulation have not been done, facilitation of expedited testing with the hematology and coagulation laboratories is critical. It should be a core competency for hematologists in training to have a thorough understanding of hemostatic laboratory tests, including interpretation of viscoelastic tests, and the evidence base guiding the care of the patient with major hemorrhage. The inclusion of the management of major hemorrhage in postgraduate training is important in improving the competency in this area.[66] The subsequent 3 cases highlight the important contributions of the consulting hematologist in supporting investigations and suggesting additional management strategies.

It is also important that hematology is involved with development and dissemination of institutional policies or guidelines for patient bleeding management, including for anemia and anticoagulation management before elective surgery or obstetrical delivery (anemia is a contributing cause for impaired hemostasis

Table 3. Brief and targeted structured questions when a consultation is requested on a refractory bleeding patient from the bedside team

No.	Component of care	Question
1	Hemorrhage type	What are the cause and location of the hemorrhage? • Traumatic injury with shock or traumatic brain injury is more likely to have hemostatic failure • Gastrointestinal tract hemorrhage rarely needs more than RBC transfusions • Cardiac surgery and postpartum hemorrhage may need higher fibrinogen targets
2	Microvascular bleeding	Is there diffuse bleeding at the surgical site or other areas suggesting profound hemostatic failure? • Prioritize hemostatic laboratory testing and components (plasma, platelets, and cryoprecipitate) or hemostatic concentrates when diffuse bleeding is observed
3	Definitive hemorrhage control	Has definitive hemorrhage control been obtained, or is there a clear pathway to achieve this goal (eg, return to operating room, on route to interventional radiology, or planned immediate hysterectomy)? • Hemostatic resuscitation should be viewed as a bridge to definitive hemorrhage control
4	Ongoing bleeding	What is the estimated current hourly blood loss? • The pace of hemorrhage should triage patients to either a multiple component strategy (brisk hemorrhage) or a sequential algorithm-based approach (controlled hemorrhage)
5	Hemodynamics	How hemodynamically unstable is the patient, and what is the pH and lactate? • Patients with hemodynamic instability are more likely to develop coagulopathy from shock and require an aggressive hemostatic response
6	Antiplatelets or anticoagulants	Was the patient on antiplatelets or anticoagulants, and have attempts been made to reverse these effects? • Prompt reversal is indicated in patients with major hemorrhage
7	TXA	Was a complete dose of TXA given either preoperatively or within 60 min of injury/hemorrhage onset? • In most bleeding scenarios, TXA improves both patient important outcomes and laboratory tests of coagulation
8	Transfusion volume	What has been transfused, and what products are currently at the bedside? • The number transfused to date provides information about the rate of hemorrhage and the sufficiency of the hemostatic support • The number of products at the bedside informs the transfusion medicine preparedness and whether the blood bank should be asked to prepare additional products
9	Measures of hemostasis	When was the last set of hemostatic tests drawn, and what were the results (including viscoelastic testing if available)? • The timing and results will dictate recommendations for additional hemostatic transfusions and investigations
10	Hemoglobin level	What is the most recent hemoglobin level? • The goal should be to keep the hemoglobin in a safe range throughout resuscitation to prevent under resuscitation and overresuscitation
11	Platelet count	What is the most recent platelet count? • The platelet count must be maintained at >50 000 × 10^6/L throughout resuscitation for all patients and higher for patients with rapid hemorrhage or brain/spine injury
12	Temperature	Is the patient hypothermic? • Hypothermia is associated with worse patient outcomes and greater blood loss

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and transfusion),[67] PPH prevention,[68] transfusion algorithms for high blood loss surgeries (eg, cardiac),[54] and massive hemorrhage.[41] The hematology service needs to be involved in their creation, dissemination (education and simulation), and efforts to ensure high rates of adherence (quality metric data collection[41]). The promotion of a collaborative team approach for planning and reviewing the management of complex patients at risk for or with major hemorrhage can be invaluable for quality assurance and improvement purposes.

Evaluation and management of patients with a life-threatening hemorrhage

Case 1: acute hemorrhage in a patient with traumatic injury

A 68-year-old pedestrian struck by a vehicle at high speed is transported by helicopter to a trauma center for definitive surgical control of hemorrhage. She has a head injury with a bleeding scalp laceration and decreased Glasgow Coma Score of 9, with high suspicion for traumatic brain injury. During transport, she is hypotensive (systolic blood pressure, 60-65 mm Hg) and tachycardic (heart rate, 120-130 beats per minute). She is administered 500 mL of crystalloid and 2 units of RBCs during transport, without hemodynamic improvement. On arrival to the hospital (43 minutes after injury), the massive hemorrhage protocol is activated as her Assessment of Blood Consumption score is 3 (systolic blood pressure < 90 mm Hg, heart rate > 120 beats per minute, and +focused assessment with sonography in trauma [FAST]).[69] She is noted to have multiple other injuries in addition to the traumatic brain injury, including a hemothorax and a pelvic fracture with a retroperitoneal hematoma. Hemostatic laboratory tests, including viscoelastic testing, are drawn at 72 minutes after injury. Initial resuscitation is commenced with a formula-based resuscitation (2:1:1 units of RBC to plasma to platelets). TXA, 1 g, is administered at 95 minutes. Despite the formula-based transfusion strategy, the patient continues to have profuse bleeding from her stapled and bandaged scalp laceration and her central line insertion site. She is being transported to interventional radiology for embolization of bleeding pelvic vessels. You receive a page from the interventional radiology suite from the Trauma Team Leader requesting your help with navigating a coagulation testing problem. The coagulation laboratory has requested redraw of the coagulation tests as no results could be obtained (international normalized ratio [INR] > 10, partial thromboplastin time [PTT] > 150 seconds, and fibrinogen < 0.5 g/L). The baseline viscoelastic testing by rotational thromboelastometry (ROTEM) is shown in Figure 1. Her hemoglobin is 10.2 g/dL, platelet count is 106 000 × 10^6/L, pH is 7.12, and lactate is 10.3 mmol/L. Her temperature is 34.7°C. You are called at 120 minutes from injury.

Case 1: comment

This patient has hemostatic failure attributable to acute traumatic coagulopathy (Table 1), with the presence of marked hypofibrinogenemia. The hemostatic derangement is consistent with the clinical scenario of major uncontrolled hemorrhage after trauma,

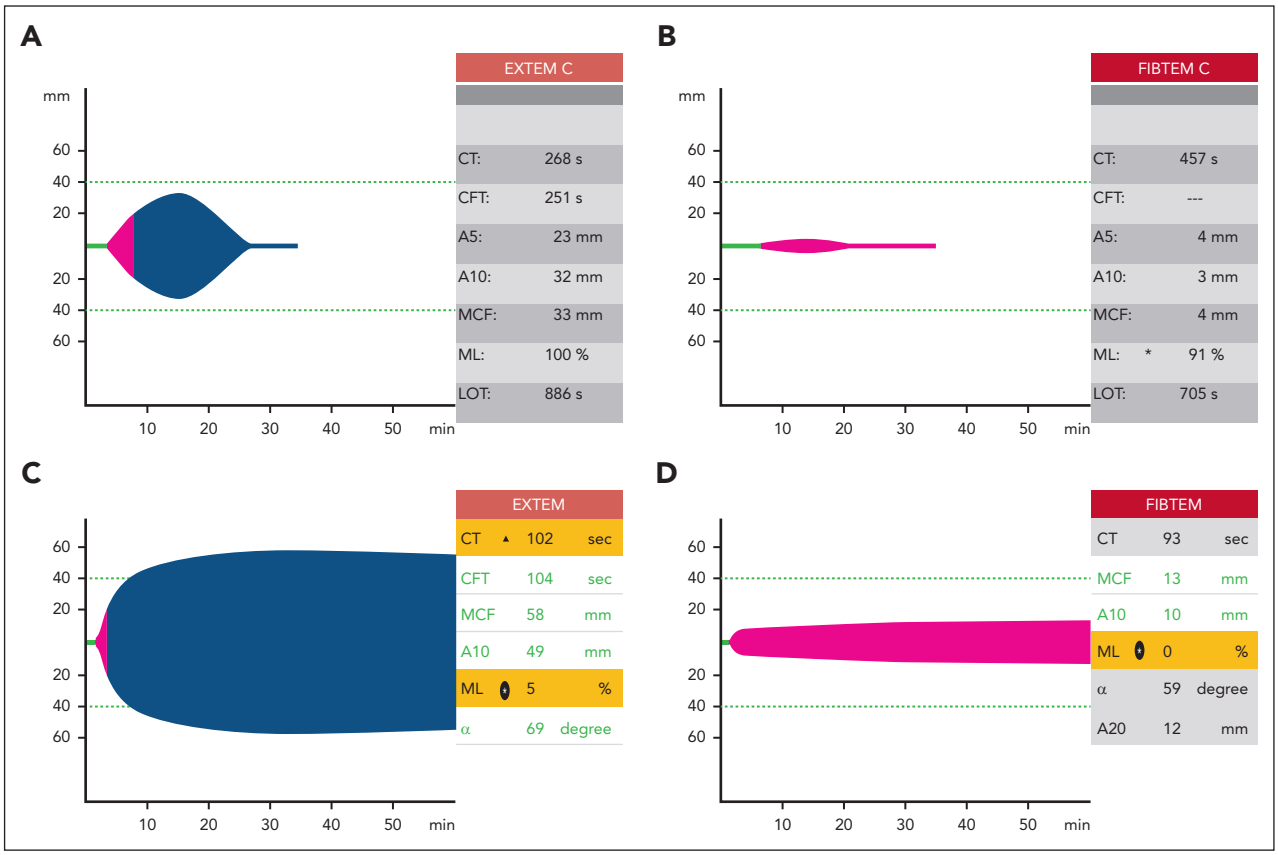

Figure 1. Results of the patient's viscoelastic testing by rotational thromboelastometry (ROTEM) in case 1. (A-B) The baseline EXTEM and FIBTEM, respectively. (C-D) The EXTEM and FIBTEM, respectively, at the start of her operative procedure, after partial correction of her coagulopathy. A5, amplitude at 5 minutes; A10, amplitude at 10 minutes; CFT, clot formation time; CT, clot time; LOT, lysis onset time; MCF, maximum clot firmness; ML, maximum lysis.

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severe shock, delayed TXA administration, and hypothermia. The clinical picture of persistent bleeding from her scalp wound and central line site is also indicative of a severe hemostatic derangement. Acute traumatic coagulopathy with hyperfibrinolysis is associated with a high mortality rate of ≈80%.[70] Every effort needs to be made to achieve an INR <1.8 and fibrinogen >1.5 g/L (or normalization of viscoelastic testing). It is communicated to the Trauma Team Leader that sample redraw is not required, and the hemostatic failure should be treated immediately. The recommendation is made to administer another 1 g of TXA and 3 pools of cryoprecipitate (15 units of cryoprecipitate or the equivalent amount of fibrinogen concentrate) to increase the fibrinogen level to >1.5 g/L, 4 units of plasma, and 1 dose of platelets (with the expectation that the platelet count would decrease below 100 000 × 10^6/L because of ongoing bleeding). The bedside team should also address the acid-base abnormalities, hypocalcemia, and hypothermia that will further exacerbate her coagulopathy. The posttransfusion laboratory tests are improved, with an INR of 2.2, fibrinogen of 1.3 g/L, platelet count of 107 000 × 10^6/L, and hemoglobin of 8.9 g/dL. The posttransfusion viscoelastic testing is shown in Figure 1. Embolization is complete, the patient's hemodynamics have stabilized, and the patient is being transferred to the operating room. In anticipation of bleeding during surgery and to prevent postoperative rebleeding, you recommend transfusing an additional 4 units of plasma, to correct the prolonged EXTEM-clot time (CT) and INR, and 2 pools of cryoprecipitate, to achieve a fibrinogen level >1.5 g/L.

Hemostatic management review

There were several issues with the patient's hemostatic management. First, there was a delay to administering TXA, which should have been prioritized within the first 60 minutes of injury to mitigate hyperfibrinolysis that can result in severe hypofibrinogenemia.[38] TXA has the greatest survival benefit if administered within 60 minutes of injury.[71,72] TXA is not associated with a clinically significant increase in thromboembolic events in the setting of trauma.[73] Increasing patient age is also not associated with an increase in thromboembolic events in the trauma setting after TXA administration.[74] Last, administration of a single dose of 2 g of TXA is effective, is not associated with safety concerns, and reduces the logistical burden of 2 doses.[75,76] A single 2-g bolus infusion was used in a large prehospital traumatic brain injury study without safety concerns (345 patients randomized to the 2-g bolus arm of the study).[75]

Second, hemostatic laboratory tests should also have been prioritized to more rapidly assess the degree of hemostatic derangement and expedite targeted hemostatic treatments. The coagulation laboratory had failed to follow the protocol for rapid release of results despite no clot found. This laboratory strategy has been validated and found to be safe.[42]

Last, hypothermia, shock, and metabolic abnormalities were not adequately addressed, likely because of competing priorities during her initial resuscitation. These factors are known to be prognostically important, and their management needs to be prioritized.[77]

Case 2: acute hemorrhage after cardiopulmonary bypass

You receive a page from the operating room to provide advice regarding the indication and dosing of recombinant activated factor VII (rFVIIa) for the management of refractory bleeding after cardiopulmonary bypass (CPB) in an 80-kg man with an acute type A aortic dissection, who is undergoing emergency aortic valve and aortic hemiarch replacement. His medications include antihypertensive drugs and acetylsalicylic acid. On presentation, he was stable and neurologically intact. Baseline laboratory results showed anemia (hemoglobin, 12.6 g/dL), thrombocytopenia (platelet count, 145 000 × 10^6/L), elevated creatinine (125 μmol/L), and normal INR and PTT. Activated clotting time (ACT) before heparin administration was within the normal range at 102 seconds.

The surgery was complex and required 210 minutes on CPB, including 35 minutes of hypothermic circulatory arrest. He received 2 g of TXA before CPB, and a total of 60 000 IU of unfractionated heparin during surgery. Following termination of CPB and reversal of heparin with 400 mg of protamine, the ACT was 132 seconds, and massive bleeding was noted. Another 100 mg of protamine was administered, but the ACT did not improve, at which point a formula-based transfusion strategy was initiated. Over the next 45 minutes, the first set of blood products (4 units of RBCs, 2 units of plasma, and 1 dose of platelets) was administered. However, bleeding continued at a rate of 200 mL every 10 minutes. A second set of blood products was ordered, and laboratory assays were sent. At 120 minutes after CPB, when hematology was consulted, the patient was bleeding at a rate of 100 mL every 10 minutes, despite having received the second set of blood products (4 units of RBCs, 2 units of plasma, and 1 dose of platelets). Laboratory testing that was sent after the first set of blood products showed a hemoglobin of 7.2 g/dL, platelet count of 45 000 × 10^6/L, fibrinogen level of 1.1 g/L, INR of 1.9, and PTT of 39 seconds. Repeat samples had just been sent to the laboratory when you were consulted, but the results were not yet available. A recent point-of-care arterial blood gas result showed a normal pH and calcium (after 2 g of calcium chloride), and a hemoglobin of 7.5 g/dL.

Case 2: comment

The patient has had major bleeding for 120 minutes after CPB, with only a modest response to a large-volume, formula-based transfusion strategy. Ongoing bleeding in this patient may prove catastrophic as there is a direct, nonlinear relationship between the amount of transfusions and risk of major morbidity and mortality after cardiac surgery.[78,79] Because this patient is continuing to experience major hemorrhage, rapid restoration of hemostasis is paramount.

Although rFVIIa can restore hemostasis in the setting of refractory bleeding by generating a thrombin burst at sites of injury,[7,79,80] you recommend that it not be used at this time because it carries significant thromboembolic risks, and the patient continues to have major coagulation defects that are correctable with lower-risk hemostatic agents, which may avoid the need for rFVIIa or improve its efficacy should it be needed as rescue therapy.[79]

Your first recommendation is to administer a second 2-g dose of TXA as hyperfibrinolysis is a major contributor to post–cardiac surgery bleeding.[7,81] The initial 2 g (20 mg/kg) of TXA that was administered pre-CPB is consistent with the recommended low-dose regimens for prevention of hyperfibrinolysis.[7,81,82]

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However, because the initial dose was administered ≈5 hours (>2 half-lives) ago and the patient has lost the equivalent of ≈1 blood volume since then, redosing at this time is indicated to ensure that the concentration of TXA is at or above therapeutic levels.

Your next recommendation is to initiate an aggressive but targeted transfusion therapy based on the coagulation abnormalities that were present before the second set of blood products, as the second set is unlikely to have corrected the abnormalities given the continued major hemorrhage and the lack of hemoglobin increment. It is recommended to administer, in order of availability, 4 g of fibrinogen concentrate (or 10 units or 2 pools of cryoprecipitate) to increase the fibrinogen level to >2.0 g/L, 2 doses of platelets to increase the platelet count to >100 000 × 10^6/L, 3 to 4 units of plasma to a target INR ≤1.5, and RBCs (or cell-saved blood) to maintain a hemoglobin of >9.0 g/dL.

The recommended thresholds for administration of fibrinogen replacement and platelets are more liberal than those in current bleeding management guidelines.[83-85] In our view, these more liberal thresholds are warranted because this patient has excessive consumption and loss of fibrinogen and platelets attributable to the underlying condition (ie, acute aortic dissection),[86] prolonged CPB duration with circulatory arrest, presence of a new aortic graft (which absorbs fibrinogen and consumes platelets),[87] and ongoing major hemorrhage.

Similarly, the 9.0-g/dL hemoglobin target is also higher than commonly recommended restrictive thresholds of 7.0 to 9.0 g/dL[83,84] to not only allow for ongoing blood loss, but also to take advantage of the contributions of RBCs to hemostasis (which include enhanced platelet function and thrombin generation).[88,89]

Additional coagulation factor replacement is needed because the elevated INR indicates that, despite the plasma transfusions, the patient still has impaired thrombin generation because of coagulation factor deficiency, which is an important cause of bleeding in cardiac surgery.[7,10,90] Emerging evidence suggests that PCCs at a dose of 25 IU/kg may be an alternative to plasma in this setting as it may be able to better restore hemostasis without increasing the risk of thromboembolic complications,[63] in contrast to the elevated risk seen with rFVIIa.[91] A large multicountry, multicenter RCT of plasma vs PCC in cardiac surgery has completed enrollment and may provide additional clarity on their use in cardiac surgery (NCT05523297).

After the recommendations were performed, bleeding slowed to a rate that allowed for chest closure and transfer to critical care. Repeat laboratory tests before transfer show a hemoglobin of 10.5 g/dL, platelet count of 140 000 × 10^6/L, fibrinogen level of 2.1 g/L, and INR of 1.6.

Hemostatic management review

There were several deficiencies in hemostatic management of this patient. First, the prophylactic TXA dose was likely too low given the presence of multiple factors that placed the patient at high risk for massive bleeding, including the aortic dissection, baseline renal dysfunction, thrombocytopenia, antiplatelet therapy, and anemia, as well as emergency, complex surgery that requires hypothermic circulatory arrest and prolonged CPB.[86,92,93] Second, the clinical team should have assessed the coagulation status before termination of CPB to allow for goal-directed rather than formula-based transfusion management. Ideally, coagulation assessment should include viscoelastic and platelet function assays that can be conducted on heparinized samples, providing timely and specific results that can be addressed immediately after CPB.[7,54] If viscoelastic testing is not available, then platelet count and fibrinogen level can, in some centers, be conducted on CPB. The Clauss fibrinogen uses both a high dilution (1:10) and a high concentration of thrombin, mitigating some of the heparin interference, but the result should be interpreted with caution with high levels of heparin.[94] Third, the post-CPB coagulation status should be measured frequently (every 30-60 minutes) to guide hemostatic therapy. Last, the focus should be on normalizing hemostasis as rapidly as possible rather than minimizing transfusions, which entails the use of liberal rather than conservative transfusion thresholds.

Case 3: acute hemorrhage after obstetrical delivery

The anesthesiologist on labor and delivery calls you for advice with an obstetric hemorrhage in a patient who is in interventional radiology for uterine artery embolization. The patient is a 36-year-old (body mass index, 41 kg/m^2) gravida 4, para 3 woman who had a vaginal birth of twins 2 hours ago. Her obstetric history includes a cesarean delivery for breech presentation, followed by 2 vaginal deliveries. Her third delivery had a mild PPH (1100 mL) attributable to uterine atony. During that delivery, she received additional uterotonics and 1 g of TXA but did not require any surgical intervention or transfusion. This twin pregnancy was complicated by preeclampsia, requiring admission to the hospital at 35 weeks' gestation. On admission, her blood pressure was 162/90 mm Hg, alanine aminotransferase was 70 U/L, lactate dehydrogenase was 550 U/L, hemoglobin was 11.5 g/dL, and platelet count was 138 000 × 10^6/L. She was started on labetalol and magnesium sulfate.

As both fetuses were cephalic presenting, an induction of labor was initiated, and she delivered 32 hours later. With delivery of the second infant, she received carbetocin, 100 μg intravenously, to prevent uterine atony, but 4 minutes after delivery, the vaginal bleeding was brisk and uterine tone unsatisfactory. During uterine massage, the anesthesiologist administered misoprostol, 200 μg sublingually, ergometrine, 250 μg intramuscularly, and 1 g of TXA. After the additional uterotonics and an ultrasound-guided curettage of the uterine cavity, tone had improved. The quantitative blood loss (QBL), the weight of blood loss in surgical materials and volume measured with a volumetric under-buttocks drape, was 2100 mL; and with ongoing bleeding, embolization of the uterine arteries was believed to be indicated. The obstetrical massive hemorrhage protocol was activated before transfer to interventional radiology, triggering the delivery of pack 1 (4 units of uncrossmatched O-negative, K-negative RBCs). RBC transfusion was commenced at 8 minutes after hemorrhage protocol activation. Before transfer to the interventional radiology, an arterial line was placed and blood samples were drawn to assess hemostasis (75 minutes from the onset of hemorrhage). A Bakri balloon was placed into the uterine cavity, and the patient was emergently transported to interventional radiology.

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While attempting uterine artery embolization, the patient's hemodynamics deteriorate, and the Bakri balloon blood reservoir measured an additional 900 mL. The laboratory testing sent before leaving the delivery suite reveal a hemoglobin of 8.1 g/dL, platelet count of 109 000 × 10^6/L, fibrinogen level of 0.8 g/L, and INR of 1.5. The bedside team concludes that a hysterectomy is required immediately because of inability to control bleeding with embolization and hemodynamic instability. The request to the consulting hematologist is to provide guidance regarding the optimal hemostatic response given the recent laboratory testing results.

Case 3: comment

Hemostatic resuscitation is paramount until surgical control of hemorrhage can be obtained via hysterectomy and to prevent rebleeding. While coordinating an emergency hysterectomy, the hemoglobin should be maintained in a safe zone (7.0-9.0 g/dL), the platelet count maintained at >50 000 × 10^6/L to 75 000 × 10^6/L, fibrinogen at >2.0 g/L, and INR at <1.8.[95] The targets for resuscitation are all based on expert opinions, derived from evidence from observation data and trials outside of postpartum hemorrhage. Although it is likely critical that the fibrinogen level is maintained >2.0 g/L during hemorrhage,[29] preemptive use of fibrinogen replacement (before fibrinogen levels are known or decrease below 2.0 g/L) has not been shown in RCTs to improve outcomes.[96] The recommended hemoglobin target during resuscitation is based on a cluster-randomized trial involving 411 trauma patients at 22 centers, finding similar outcomes when a target of 7 to 9 g/dL was compared with 10 to 12 g/dL, as no RCTs have been performed in the PPH setting.[97] The recommended INR target of 1.8 is based on expert opinion and not clinical trials; however, given the difference in clotting factor concentrations between a target of 1.5 and 1.8 is <10%, the targets of 1.5 and 1.8 may be considered equivalent.[98]

This patient opted for a vaginal delivery of twins after weighing the benefits and risks, particularly in light of her multiple risk factors for PPH, including a prior cesarean delivery, history of previous PPH, multiple gestation, elevated body mass index, hypertensive disorder of pregnancy, and prolonged labor of >24 hours.[99] Effective management of PPH requires a multicomponent bundled clinical intervention focused on risk assessment, immediate readiness, active third-stage management, and early intervention.[100] Early detection of PPH and use of bundled treatment reduce the incidence of severe PPH, need for surgical intervention, and death.[101]

Transition from routine postpartum bleeding to PPH (QBL, >1000 mL) can be abrupt, rapidly escalating to multiorgan dysfunction and death. Underestimating blood loss and the severity of PPH leads to treatment delays. Traditional nonquantitative estimates of blood loss underestimate blood loss. Accurate monitoring with QBL is essential for longitudinal risk assessment after delivery. Given this patient's multiple risk factors for PPH, preparation with all potentially needed materials and medications should be made in advance of delivery; these include dual intravenous access, RBC availability, pharmaceuticals (uterotonics, TXA), and medical devices (Bakri balloon).

Compared with placebo, ergometrine, carboprost, or misoprostol, oxytocin is the drug of choice for the active management of the third stage of labor. The other agents are adjunctive for the treatment of uterine atony and PPH. Carbetocin is a synthetic, long-acting analogue of oxytocin with equivalent affinity for the oxytocin receptor. Prophylactic carbetocin, 100 μg intravenously given over 30 to 60 seconds, provides similar or better clinical effects compared with oxytocin.[95]

An additional hemostatic adjunct to uterotonics is TXA. Despite mixed findings of RCTs of prophylactic or treatment TXA, it remains a guideline recommendation based on its benefit-to-risk considerations.[102-104] TXA should be considered whenever a second-line adjunctive uterotonic is administered prophylactically in patients at high risk of PPH, such as in this case with multiple PPH risk factors. A second dose of 1 g should be considered 30 minutes after the initial dose if bleeding is not controlled.

Emergent uterine artery embolization is an effective method in the management of PPH. If hemodynamically stable with persistent low-volume bleeding, uterine artery embolization is able to achieve hemostasis and reduce the incidence of hysterectomy.[105,106] Uterine artery embolization can also reduce blood loss if a hysterectomy is still necessary to treat the atony and ongoing PPH. It should also be considered after hysterectomy in rare cases with persistent bleeding.

Hemostatic management review

Several issues with hemostasis management were noted with this case. First, the patient was at high risk for a PPH, and a predelivery multidisciplinary review with the team should have been conducted to ensure adequate preparation in the event of PPH (eg, prophylactic TXA, ensuring all medications and devices were on hand, and cell saver setup on hand[107]). Second, the patient's bleeding was likely too brisk for consideration of uterine artery embolization. In cases of massive PPH, where basic resuscitation and hemodynamic management cannot stabilize the patient, a hysterectomy should not be delayed. Uterine artery embolization requires transporting the patient to a less ideal environment for anesthesia and resuscitative efforts, so only reasonably stable patients should be considered for uterine artery embolization. Third, failure to monitor the fibrinogen level early and frequently (every 30-60 minutes)[40] may have delayed the achievement of hemostasis because of the decrease in the level to <2.0 g/L.

Summary

Managing the hemostatic response to acute, life-threatening hemorrhage is an important competency for all consulting hematologists. The clinical response to a bleeding patient is challenging, often with key treatments or tests inadvertently delayed or missed because of the sheer number of tasks required. This article provides a review of these pitfalls to assist the consulting hematologist. Through these varied case vignettes, we have highlighted the importance of considering the clinical context, the rate of hemorrhage, pharmaceutical adjuncts, and laboratory test results in decision-making. In all cases of major hemorrhage, obtaining surgical or radiologic control of bleeding is paramount. The hematologist plays an important communication role between the clinical team and both the coagulation and blood bank laboratories. In cases such as these, an aggressive

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liberal (and as much as possible, personalized) approach to hemostatic replacement is favored to assist with rapid bleeding control to mitigate the downstream morbidity of hemodynamic instability from ongoing hemorrhage.

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Footnote

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